HETEROCYCLES, Vol. 65, No. 8, 2005, pp. 1821 - 1827
Received, 1st March, 2005, Accepted, 30th June, 2005, Published online, 1st July, 2005

HIGH THROUGHPUT SYNTHESIS OF PYRAZOLOPYRIMIDINES *VIA* COPPER- CATALYSED CYCLIZATION AND X-RAY STUDY

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Abstract –A rapid and easy high-yielding synthesis of pyrazolopyrimidinones in the presensce of copper chloride is described. To fully confirm the structure of a Viagra® intermediate, the X-Ray structure of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (**2a**) was determined.

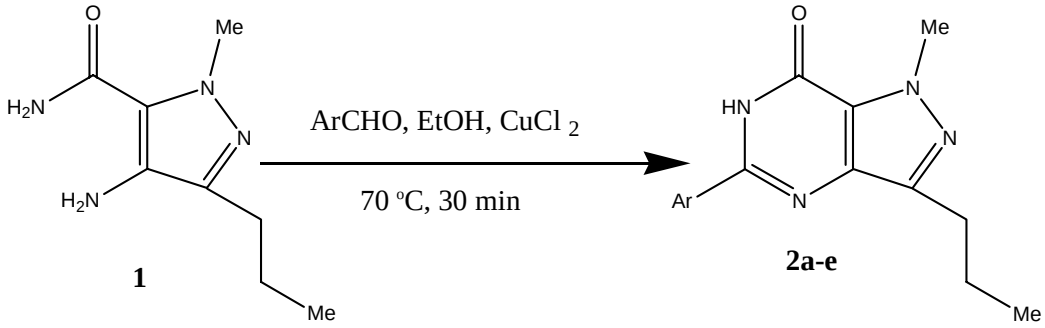
INTRODUCTION

The synthesis of pyrazolopyrimidines has attracted considerable interest in pharmaceutical research due to their therapeutic potentials, especially as phosphodiesterase inhibitors.[1] Viagra®, the orally active agent for the treatment of male erectile dysfunction (MED), is a well-known selective phosphodiesterease type 5 (PDE5) inhibitor.[2] We have recently disclosed a novel series of new and selective phosphodiesterase type 5 (PDE5) inhibitors [3-6] which show significant activity in MED. Moreover, two of us have developed an efficient and novel method for the construction of quinazolinones[6] using a copper chloride-mediated reaction. Extending the potential of this new cyclization method, we planned to exploit this reaction for the synthesis of pyrazolopyrimidines.

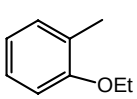
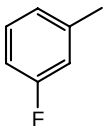
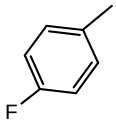
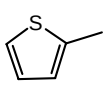
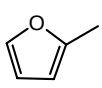
RESULTS AND DISCUSSION

We began our investigations by performing the reaction of **1** [7] with 2-ethoxybenzaldehyde in the presence of one equivalent of copper chloride in refluxing ethanol (Scheme 1). The reaction needed 8 hours for completion. However, increasing the equivalents of copper chloride causes a significant decrease in reaction time (Table 1, Entries 1 – 5), and using five equivalents of copper chloride gives the pyrazolopyrimidine derivative (**2a**) within 30 min in 89% yield.

Applying the latter conditions using substituted aldehydes yielded the pyrazolopyrimidinones (**2b-e**) in 82–89 % yield (Table 1, Entries 6 – 9). Neither a change of the solvent nor of the equivalents in aldehydes (Table 1, Entries 10, 11) show any significant effect on the yield of the reaction. Only by careful crystallization of the precipitated products the pyrazolopyrimidinones could be isolated in high purity and traces of copper salts were removed by bubbling hydrogen sulfide gas through the hot reaction mixture for 10 min followed by hot filtration to remove the precipitated copper sulfide. Surprisingly, the reaction of **1** with 2-pyridylcarbaldehyde did not give the expected pyrazolopyrimidinone, but instead an organometallic compound, the structure of which is under investigation. Analyses of the pyrazolopyrimidinones (**2a-e**) gave identical results as reported in the literature [7]. Physical data for the pyrazolopyrimidinones (**2a-e**) are given in Table 2.



1 **2a-e**

No.	**a**	**b**	**c**	**d**	**e**
Ar					

Scheme 1

The structure of **2a** is also confirmed by single crystal X-Ray crystallography. Figure 1 shows the ORTEP diagram, details of X-Ray data collection and refinement, bond distances and angles are collected in Tables 2 and 3. A salient feature of the structure of **2a** is the almost co-planarity of the 2-ethoxyphenyl residue to the pyrimidinone ring.

In conclusion, this simple and high-yielding method for the construction of pyrazolopyramidinone ring systems using a copper-mediated reaction gives an improved access for the synthesis of Viagra®, used worldwide as an efficacious, orally active agent for the treatment of male erectile dysfunction (MED) as well as to the synthesis of new pyrazolopyrimidinones with potential phosphodiesterease type 5 (PDE5) inhibitors.

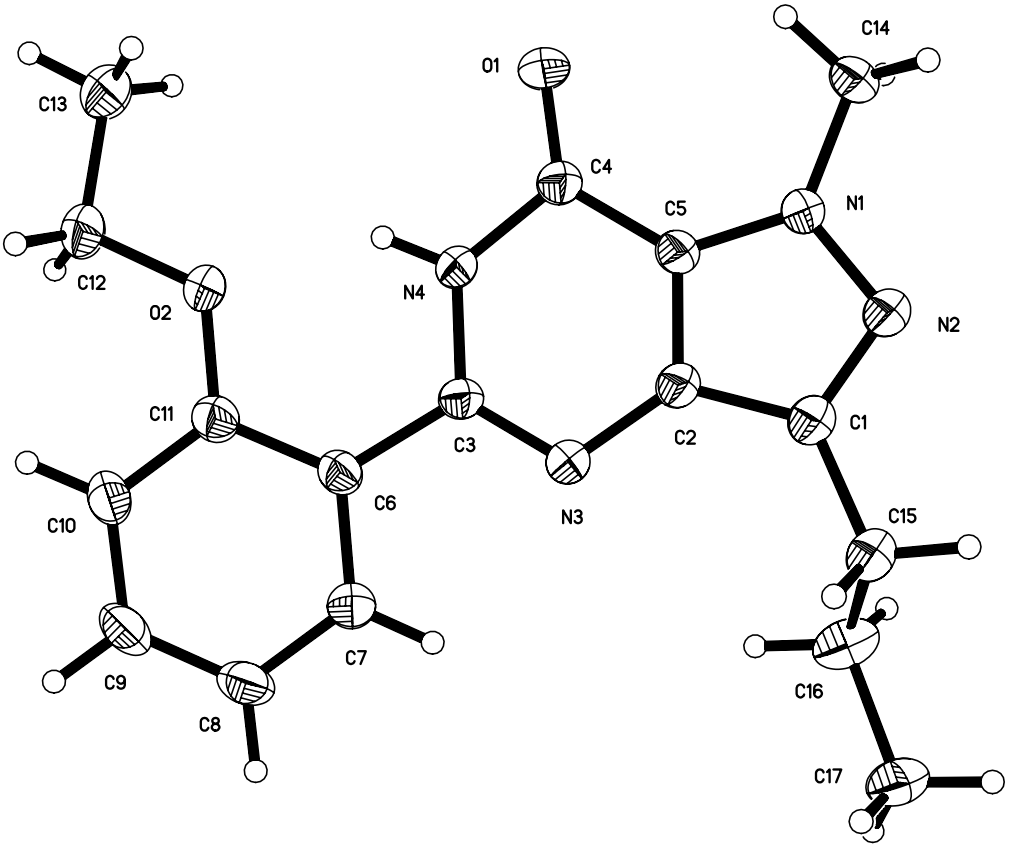


Figure 1. ORTEP diagram of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-*d*] -pyrimidin-7-one (**2a**).

EXPERIMENTAL

Materials and instrumentation: ^{1}H NMR spectra were measured on a Bruker AM 250 FT spectrometer operating at 300 K and using TMS as internal standard. MS spectra (electron impact) were obtained on a Varian CH-7 spectrometer at 70 eV at an ion source temperature of 200°C. Melting points were recorded on an electrothermal melting temperature apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer elemental analyzer, model 240. Aryl aldehydes were purchased from Aldrich and used without further purification. The crystal structure of compound (**2a)** was determined by

single X-Ray diffraction method. Preliminary examination and data collection were performed *via* Cu-K_α radiation (λ = 1.54056 Å) on an ENRAF-NONIUS CAD4 diffractometer operating in the omega scan mode. The initial position for all non-hydrogen atoms were obtained by using direct methods of the SHELXL-97 program.[8] Positional and displacement parameters for non-hydrogens atoms were refined using a full-matrix least-squares refinement procedure. Atomic position of hydrogen atoms were determined from a difference Fourier map and refined isotropically.

Table 1. Reaction conditions and yields for compounds (**2a – e)**

Entry	Compd No.	Ar	Reaction conditions	Yield (%)
1	**2a**	*o*-Et*O*C_6H_4	1 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 8 h	73
2	**2a**	*o*-Et*O*C_6H_4	2 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 3 h	82
3	**2a**	*o*-Et*O*C_6H_4	3 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 1 h	84
4	**2a**	*o*-Et*O*C_6H_4	4 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 50 min	88
5	**2a**	*o*-Et*O*C_6H_4	5 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 30 min	89
6	**2b**	*m*-FC_6H_4	5 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 30 min	85
7	**2c**	*p*-FC_6H_4	5 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 30 min	87
8	**2d**	2-thienyl	5 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 30 min	84
9	**2e**	2-furyl	5 equiv. $CuCl_2$, 1.1 equiv. ArCHO, ethanol, 30 min	82
10	**2a**	*o*-Et*O*C_6H_4	5 equiv. $CuCl_2$, 3 equiv. ArCHO, propanol, 30 min	87
11	**2a**	*o*-Et*O*C_6H_4	5 equiv. $CuCl_2$, 3 equiv. ArCHO, methanol, 30 min	76

General procedure for the synthesis of pyrazolopyrimidinones (**2a–e**):

A mixture of **1** (182 mg, 1 mmol), the corresponding aryl aldehyde (1.1 mmol) and $CuCl_2$ (664 mg, 5 mmol) in ethanol (10 mL) was heated under reflux for 30 min. Hydrogen sulfide gas was then bubbled through the hot reaction mixtures for 10 min and the dark precipitate was filtered off. Cooling the clear filtrate afforded the title compounds *via* crystallization from ethanol. The physical and spectroscopic data of compounds (**2a–e)** (melting points, NMR, MS) are in agreement with those reported in the literature.[6]

Table 2. Details of X-Ray data collection and refinement for compound (**2a**)

Empirical formula	$C_{17}H_{20}N_4O_2$
Formula weight	312.37
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Triclinic, *P-1*
Unit cell dimensions	
a (Å)	9.229(5)
b (Å)	9.5197(17)
c (Å)	10.281(3)
α (°)	63.777(13)
β (°)	88.70(5)
Volume (Å^3)	783.5(5)
Z, Calculated density (g/cm^3)	2, 1.324
Absorption coefficient (mm^{-1})	0.090
F(000)	332
Crystal size (mm)	0.4 × 0.2 × 0.1
Limiting indices, *hkl*	-11 to 1, -10 to 10, -13 to 13
Reflections collected / unique	4058 / 3419 [*R(int)* = 0.0298]
Completeness to θ = 27.50°	95.1%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3419 / 0 / 216
Goodness-of-fit on F^2	1.037
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0521, wR_2 = 0.1313
R indices (all data)	R_1 = 0.0752, wR_2 = 0.1448
Extinction coefficient	0.021(5)
Largest diff. peak and hole	0.291 and -0.243 (e·A^{-3})

Table 3. Bond lengths [Å] and angles [deg] for **2a**

O(1)-C(4)	1.226(2)	C(1)-N(2)-N(1)	106.72(15)
O(2)-C(11)	1.366(2)	C(3)-N(3)-C(2)	114.63(15)
O(2)-C(12)	1.438(2)	C(3)-N(4)-C(4)	126.60(16)
N(1)-C(5)	1.347(2)	N(2)-C(1)-C(2)	109.54(16)
N(1)-N(2)	1.360(2)	N(2)-C(1)-C(15)	121.77(17)
N(1)-C(14)	1.450(2)	C(2)-C(1)-C(15)	128.66(17)
N(2)-C(1)	1.331(2)	N(3)-C(2)-C(5)	124.37(17)
N(3)-C(3)	1.302(2)	N(3)-C(2)-C(1)	129.83(16)
N(3)-C(2)	1.377(2)	C(5)-C(2)-C(1)	105.76(16)

N(4)-C(3)	1.381(2)	N(3)-C(3)-N(4)	123.09(16)
N(4)-C(4)	1.384(2)	N(3)-C(3)-C(6)	118.31(15)
C(1)-C(2)	1.411(3)	N(4)-C(3)-C(6)	118.60(16)
C(1)-C(15)	1.501(3)	O(1)-C(4)-N(4)	121.11(16)
C(2)-C(5)	1.386(2)	O(1)-C(4)-C(5)	129.20(17)
C(3)-C(6)	1.479(2)	N(4)-C(4)-C(5)	109.69(15)

Table 3 continued

C(4)-C(5)	1.436(3)	N(1)-C(5)-C(2)	106.78(16)
C(6)-C(7)	1.398(2)	N(1)-C(5)-C(4)	131.55(16)
C(6)-C(11)	1.412(3)	C(2)-C(5)-C(4)	121.61(16)
C(7)-C(8)	1.376(3)	C(7)-C(6)-C(11)	117.93(16)
C(8)-C(9)	1.378(3)	C(7)-C(6)-C(3)	116.66(16)
C(9)-C(10)	1.384(3)	C(11)-C(6)-C(3)	125.41(16)
C(10)-C(11)	1.386(3)	C(8)-C(7)-C(6)	121.69(18)
C(12)-C(13)	1.500(3)	C(7)-C(8)-C(9)	119.31(18)
C(15)-C(16)	1.507(3)	C(8)-C(9)-C(10)	121.01(18)
C(16)-C(17)	1.530(3)	C(9)-C(10)-C(11)	119.82(18)
		O(2)-C(11)-C(10)	121.80(17)
C(11)-O(2)-C(12)	119.45(15)	O(2)-C(11)-C(6)	117.99(16)
C(5)-N(1)-N(2)	111.19(15)	C(10)-C(11)-C(6)	120.21(17)
C(5)-N(1)-C(14)	128.58(16)	O(2)-C(12)-C(13)	107.00(16)
N(2)-N(1)-C(14)	120.17(15)	C(1)-C(15)-C(16)	113.75(17)
		C(15)-C(16)-C(17)	111.53(19)

5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (2a)

Yield (265 mg) 85%; mp 144–145 °C. *Anal.* Calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.30; H, 6.44; N, 17.91; MS-EI *m/z* 312 (M^+); ^{1}H NMR ($CDCl_3$): δ=1.04 (t, *J* = 7.3 Hz, –$CH_2CH_2CH_3$), 1.60 (t, *J* = 7.0 Hz, –OCH_2CH_3), 1.88 (m, –$CH_2CH_2CH_3$), 2.93 (t, *J* = 7.9 Hz, –$CH_2CH_2CH_3$), 4.30 (q, *J* = 7.0 Hz, –OCH_2CH_3), 4.27 (s, N1–CH_3), 7.03–8.46 (m, C_6H_4), 11.13 (br s, –N*H*).

5-(3-Fluorophenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (2b)

Yield (255 mg) 89%; mp 188–190 °C *Anal.* Calcd for $C_{15}H_{15}N_4OF$: C, 62.93; H, 5.28; N, 19.57. Found: C, 62.99; H, 5.22, N, 19.55; MS–EI *m/z* = 286 (M^+); ^{1}H NMR ($CDCl_3$): δ=1.02 (t, *J* = 7.3 Hz, –$CH_2CH_2CH_3$), 1.75 (m, –$CH_2CH_2CH_3$), 2.73 (t, *J* = 7.6 Hz, –$CH_2CH_2CH_3$), 4.21 (s, N1–CH_3), 7.16–7.57 (m, C_6H_4),11.75 (br s, –N*H*).

5-(4-Fluorophenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (2c)

Yield (260 mg) 91%; mp 241–242 °C. *Anal.* Calcd for $C_{15}H_{15}N_4OF$: C, 62.93; H, 5.28; N, 19.57. Found: C, 62.89; H, 5.26; N, 19.53; MS–EI *m/z*=286 (M^+); ^{1}H NMR ($CDCl_3$): δ=1.02 (t, *J* = 7.3 Hz, –$CH_2CH_2CH_3$), 1.85 (m, –$CH_2CH_2CH_3$), 2.89 (t, *J* = 7.4 Hz, –$CH_2CH_2CH_3$), 4.25 (s, N1–CH_3), 7.17–8.15 (m, C_6H_4),11.75 (br s, –N*H*).

1-Methyl-3-propyl-5-thien-2-yl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (2d)

Yield (225 mg) 82%; mp 249–250 °C. *Anal.* Calcd for $C_{13}H_{14}ON_4S$: C, 56.91; H, 5.14; N, 20.42. Found: C, 56.85; H, 5.12; N, 20.37; MS–EI *m/z* = 274 (M^+); ^{1}H NMR ($CDCl_3$): δ=0.99 (t, *J* = 7.3 Hz, $-CH_2CH_2CH_3$), 1.80 (m, $-CH_2CH_2CH_3$), 2.81 (t, *J* = 7.5 Hz, $-CH_2CH_2CH_3$), 4.19 (s, N1–CH_3), 7.10 (dd, *J* = 4.0, 5.2 Hz, 1H-th), 7.54 (dd, *J* = 0.9, 5.2 Hz, 1H-th), 8.07 (dd, *J* = 0.9, 4.0 Hz, 1H-th), 12.31 (br s, –N*H*).

5-Furan-2-yl-1-methyl-3-propylyl-1,6-dihydropyrazolo[4,3-*d*]pyrimidin-7-one (2e)

Yield (222 mg) 86%; mp 228–229 °C. *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.39; found: C, 60.42; H, 5.44; N, 21.40; MS–EI: *m/z* = 258 (M^+); ^{1}H NMR ($CDCl_3$): δ=0.97 (t, *J* = 7.3 Hz, $-CH_2CH_2CH_3$), 1.78 (m, $-CH_2CH_2CH_3$), 2.79 (t, *J* = 7.5 Hz, $-CH_2CH_2CH_3$), 4.17 (s, N1–CH_3), 6.62 (dd, *J* = 1.8, 3.6 Hz, 1H-fu), 7.48 (dd, *J* = 0.8, 3.5 Hz, 1H-fu), 7.82 (dd, J=0.8, 1.8 Hz, 1H-fu), 12.30 (br s, –N*H*).

ACKNOWLEDGEMENTS

We are grateful to the Hashemite University for financial support. We express our gratitude to Internationales Büro of BMBF, Jülich, for a fellowship granted to Dr. R. J. A.-J.

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